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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/120,970	07/22/98	CURTISS R	MEGAN-100CON

EXAMINER	
PORTNER, V	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary	Application No. 09/120,970	Applicant(s) Curtiss et al
	Examiner Portner	Group Art Unit 1645

☒ Responsive to communication(s) filed on *Jun 15, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *30-33 and 35-64* is/are pending in the application.

Of the above, claim(s) *45* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *30-33, 35-44,46-64 (elected species)* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *30-33 and 35-64* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 30-33 and 35-64 are pending.

Election/Restriction

1. Applicant's election without traverse of species asd and P22 genes 13 and 19 in Paper No. 11 is acknowledged. Claims which recite non-elected inventions will not be examined and stand withdrawn from consideration at this time.

Please Note: Non-elected species of invention in claims 40, 44 and 45 will not be examined at this time.

Information Disclosure Statement

2. The information disclosure statement submitted January 24, 2000 has been considered prior to first action.

Claim Rejections - 35 U.S.C. § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 30-33 and 35-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the induction of a protective immune response using transformed Salmonella host cells (dependent claim 37) that comprise an environmentally limited viability system, that may express an antigen wherein the cell would comprise either lethality genes or the combination of an essential gene and lethality genes, the essential gene being an Asd negative mutant and the lethality genes being Salmonella bacteriophage P22 lysis genes 13 and 19, does not reasonably provide enablement for the use of **any** microbial cell administered by **any** mode of administration, of **any** amount, for **any** antigen to induce a protective immune response against the microbial cell or the antigen it expresses, The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims are being read to encompass the administration of a vaccine composition to a warm blooded animal for induction of a protective immune response, albeit a prophylactic or therapeutic immune response.

The specification fails to teach how to formulate and use the claimed vaccines using any host cell that would comprise the Salmonella bacteriophage P22 genes 13 and 19, together with Asd negative mutation that would also express a heterologous antigen. There is no suggestion and teaching in the prior art to use any other host cell other than Salmonella together with Salmonella bacteriophage late genes. No showing has been provided to show that the Salmonella

bacteriophage genes would function to limit viability in any host cell other than Salmonella, and to show that the host cell would function as a vaccine vector.

The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to infection or disease induction. The specification teaches that the claimed microbial cell that may express an antigen will induce or elicit antibodies.

The specification does not provide substantive evidence that the method of inducing immunoprotection through administration of the vaccine is capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the microbial cells for their intended purpose of preventing infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced. The claims encompass the expression of an HIV viral antigen in the microbial cell. No HIV vaccines have been shown to induce an immunoprotective immune response in a warm blooded animal.

The ability to reasonably predict the capacity of a single immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic. Ellis exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of the at protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies"(page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody

response fail to elicit in vivo protective immunity. See Boslego et al. wherein a single gonococcal pillin protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

The specification fails to teach how any expressed antigen of any size or type would be capable of inducing protective immunity. Further, the specification fails to provide guidance on how to select those nucleic acid sequences for all of the antigens that could be expressed in a microbial cell that would induce a protective immune response, the skilled artisan would be required to de novo locate, identify and characterize the claimed antigens by their nucleic acid sequences and what portions of the nucleic acid sequences would encode for antigens that would induce a protective immune response. This would require undue experimentation given the fact that the specification is completely lacking in teachings as to what these nucleic acids are, or the amino acids that would be encoded by the nucleic acid sequences that would be expressed by the microbial cell. The person of skill in the art could not use the invention commensurate in scope with these claims

6. Claim 61 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth below.

It is apparent that the claimed plasmid is required to practice the claimed invention. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the vector, see 37 C.F.R. 1.802.

The specification does not provide a repeatable method for obtaining pMeg-104 and it does not appear to be a readily available material. The encoded nucleic acid sequences contained within the plasmid are not disclosed in the instant Application. Deposit of the vector would satisfy the enablement requirements of 35 U.S.C. 112.

An affidavit or declaration by Applicants, or a statement by an attorney of record stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CAR 1.801-37 CAR 1.809.

7. Claims 30-33 and 35-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30-33 and 35-64 recite an incomplete method. The method only recites a single method step of administering the composition to an animal. No correlation step is provided. The method does not recite a step that distinctly defines the method as inducing immunoprotection and is therefore omits essential methods steps.

Claims that recite abbreviations without the abbreviation first being defined in the claims do not distinctly claim Applicant's invention, specifically claims: 43, 44, 47 51,53-55 and 60.

Claim 51 recites the phrase "and promoter elsewhere in the cell". What this phrase is defining or claiming is not clearly recited.. A single promoter is defined to be virB that is in association with virF. How an additional promoter is in relationship with the virB promoter is not distinctly claimed. The claim also recites an improper Markush group. Clarification is requested.

Double Patenting

8. Applicant is advised that should claims 30-31 be found allowable, claims 12 or 13 will be objected to under 37 CAR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 30 is being read as including one embodiment, specifically an essential gene, asd.

Claim Rejections - 35 U.S.C. § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Please Note: For purposes of Applying prior art:

a. Claims 30-33, 35-38, 48-64 will be read as microbial cells that comprise: an essential gene or a lethal gene or the combination of an essential and lethal gene, in light of the elected species.

b. Claims 39-46 must have the combination of both an essential gene and a lethal gene, specifically an asd nucleic acid sequence and P22 genes 13 and 19 with the recited functionality.

c. Claims 31-32 and 64-65 also comprise and express an expression gene.

10. Claims 30-33,35-38,48-49 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakayama et al (1988) **or** Curtiss et al (1989).

Nakayama et al disclose a method of administering a microbial cell that comprises an expression antigen, wherein the microbial cell is an avirulent Salmonella strain with a trc promoter, and attenuated through asd, cya and crp mutations (see page 694, col. 1, paragraph 2), the expression gene encoded a Streptococcus mutans Protein-A antigen. The mutant strain was administered to a warm blooded animal perorally (see page 696, col.1, Animal infectivity studies). The loss of the Asd^+ plasmid would result in cell death outside the host animal in the absence of supplemental DAP. Therefore, Nakayama anticipates the now claimed invention.

Curtiss et al(1989) disclose a method of administering a microbial cell that comprises an expression antigen, wherein the microbial cell is an avirulent Salmonella strain with a trc promoter, and attenuated through asd, cya and crp mutations (see abstract, page 591, last sentence and page 592, bottom of page), the heterologous expression gene encoded Streptococcus mutans Protein-A. The mutant strain was administered to a warm blooded animal perorally (mice, page 593, first paragraph). The loss of the Asd^+ plasmid would be in the absence of supplemental DAP resulting in cell death outside the host animal. Therefore the reference anticipates the now claimed invention.

11. Claims 30-33,35-38, 48-49 and 65 are rejected under 35 U.S.C. 102(e) as being anticipated by Curtiss, III (US Pat. 5,672,345) .

The reference discloses and claims a method of stimulating an immune response utilizing an Asd-negative mutant that can express a heterologous antigen. The reference teaches and claims the use of avirulent Salmonella strains for use in a method of inducing an immune response in a warm blooded animal. The reference anticipates the now claimed invention.

12. Claims 30-33,35-38 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Jagusztyn-Krynicka et al (1993).

Jagusztyn-Krynicka et al (1993) disclose a method of administering a microbial cell that comprises expression antigens, wherein the microbial cell is an avirulent Salmonella strain. The Salmonella strains were attenuated through asd, cya and crp mutations (see abstract), the heterologous expression genes encoded both E.coli and S.sobrinus antigens. Two of the mutant constructs are being evaluated for immunogenicity. In order to obtain an immune response, the microbial cell that expresses the antigen is administered to a warm blooded animal. Inherently the reference discloses a method of inducing an immune response in a warm blooded animal (see page 1013, col. 1, last paragraph). The loss of the Asd^+ plasmid would be in the absence of DAP resulting in cell death outside the host animal. Therefore the reference anticipates the now claimed invention.

13. Claims 30-33,35-38 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Gentry-Weeks et al (1992).

Gentry-Weeks et al disclose a method of administering a microbial cell that comprises an expression antigen, wherein the microbial cell is an avirulent E.coli or Salmonella strain. The E.coli strains were asd$^-$ negative (see Table 1, E.coli K-12 stains), and the Salmonella strains were attenuated through asd, cya and crp mutations (see page 7731, Table 1), the heterologous expression gene encoded a Bordetella avium antigen. The mutant strains was administered to a warm blooded animal perorally (see page7732, col.2, Immunization of turkeys). Antibodies to the Salmonella host cell were found in the animals serum post immunization (page 7737, col. 2, paragraph 1). The loss of the Asd$^+$ plasmid would be in the absence of DAP resulting in cell death outside the host animal. Therefore the reference anticipates the now claimed invention.

14. Claims 30-33,35-38 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Schodel et al (Infection Immunity, May 1994).

Schodel et al (1994) disclose a method of administering a microbial cell that comprises an expression antigen, wherein the microbial cell is an avirulent Salmonella strain. The Salmonella strains were attenuated through asd, cya and crp mutations (see abstract), the heterologous expression gene encoded a Hepatitus B virus Core-pre-S protein antigen. The mutant strains were administered to a warm blooded animal orally (see abstract, mice) and induced potentially neutralizing antibodies directed against the viral antigen. The loss of the Asd$^+$ plasmid would be

in the absence of DAP, resulting in cell death outside the host animal. Therefore, the reference anticipates the now claimed invention.

15. Claims 30-33,35-38 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Cieslak et al (1993).

Cieslak et al (1993). disclose a method of administering a microbial cell that comprises an expression antigen, wherein the microbial cell is an avirulent Salmonella strain. The Salmonella strains were attenuated through asd, cya and crp mutations (see abstract), the heterologous expression gene encoded an Entamoeba histolytica antigen. The mutant strains were administered to a warm blooded animal orally (see abstract, gerbil or mice (page 774, col. 1, second full paragraph) and induced antibodies directed against the amoebic antigen. The loss of the Asd^+ plasmid would be in the absence of DAP resulting in cell death outside the host animal. Therefore the reference anticipates the now claimed invention.

Claim Rejections - 35 U.S.C. § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 30-33, 35-38,50,52-54 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Curtiss (US Pat. 5,672,345) or Curtiss et al (1989) in view of Molin et al (US Pat. 5,702,916).

See discussion of **Curtiss (US '345)** above. The reference discloses a method of inducing an immune response utilizing an avirulent Salmonella that comprises an expression gene that encodes and antigen and teaches the importance of selective maintenance of recombinant expression genes in a population of vaccine cells through the use of an Asd mutation that under the control of promoter but differs from the instantly claimed invention by failing to show the use of a temperature regulated promoter or regulatory element.

Molin '916 teaches means and methods of constructing microbial cells that comprise both essential genes and lethal genes in the production of an environmentally limited viability system, suggests the use of temperature sensitive promoters (col. 8, lines 6-8), as well as temperature sensitive repressor cI857 in association with a PR promoter in an analogous art for the purpose of producing recombinant host cells that are safe, and growth inhibited when outside the animal host and are useful for inducing an immune response in a warm blooded animal.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to modify the promoter of Curtiss with the temperature regulated promoter of Molin because Molin teaches the importance of regulated transcription associated with cell killing function, and a successful means of accomplishing this regulatory function is through change of temperature and Molin discloses three temperature sensitive regulating factors

that are useful in microbial cells that would result in the control of expression of essential or lethal genes.

See discussion of **Curtiss et al (1989)** above. The reference discloses a method of inducing an immune response utilizing an avirulent Salmonella that comprises an expression gene that encodes and antigen and teaches the importance of selective maintenance of recombinant expression genes in a population of vaccine cells through the use of an Asd mutation that under the control of promoter but differs from the instantly claimed invention by failing to show the use of a temperature regulated promoter or regulatory element.

Molin '916 teaches means and methods of constructing microbial cells that comprise both essential genes and lethal genes in the production of an environmentally limited viability system, suggests the use of temperature sensitive promoters (col. 8, lines 6-8) in an analogous art for the purpose of producing recombinant host cells that are safe, and growth inhibited when outside the animal host and are useful for inducing an immune response in a warm blooded animal.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to modify the promoter of Curtiss with the temperature regulated promoter of Molin because Molin teaches the importance of regulated transcription associated with cell killing function, and a successful means of accomplishing this regulatory function is through change of temperature and Molin discloses three temperature sensitive regulating factors

that are useful in microbial cells that would result in the control of expression of essential or lethal genes.

18. Claims 30-33, 35-38,50,52 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Curtiss (US Pat. 5,672,345) or Curtiss et al (1989) in view of Miller et al.

See discussion of **Curtiss (US '345)** above. The reference discloses a method of inducing an immune response utilizing an avirulent Salmonella that comprises an expression gene that encodes and antigen and teaches the importance of selective maintenance of recombinant expression genes in a population of vaccine cells through the use of an Asd mutation that under the control of promoter but differs from the instantly claimed invention by failing to show the use of a temperature regulated promoter or regulatory element.

Miller et al (US Pat. 6,010,901) teaches the importance of using environmentally regulated promoters for controlled expression wherein the expression of a gene encoded antigen in an analogous art for the purpose of producing microbial cells that express a heterologous expression gene that encodes an antigen, wherein the microbial cell expresses the antigen based upon promoters in biosynthetic pathways which are turned on or off by the level of a specific component or components, e.g., iron, temperature responsive promoters (col. 5, lines 30-39) or promoters which are expressed more actively in specific cellular compartments and the expressed antigen is useful for inducing an immune response in a warm blooded animal.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to modify the promoter of Curtiss with the temperature regulated promoter of Miller et al ('901) because Miller et al ('901) teaches the importance of regulated gene expression and a temperature sensitive promoter is taught to provide for increased control of environmentally expressed gene antigens.

19. Claims 30-33,35-38,48-49, 47 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Curtiss (US Pat. 5,672,345) or Curtiss et al (1989) in view of Curtiss III (US Pat. 4,968,619).

See discussion of Curtiss '345 above. Curtiss shows a method of inducing an immune response to a microbial cell that comprises an environmentally limited viability system, wherein the essential gene is on an extrachromosomal gene and also comprises a replication gene, but differs from the instantly claimed invention by failing to show the replication gene to be polA.

Curtiss ('619) teaches the importance of environmentally regulating the expression of a gene in an analogous art for the purpose of teaching means and method of inducing an immune response to a microbial cell that depends on a characteristic of the environment in which the cell resides and to regulate replication of gene expression using polA.(see col. 3-4, col. 6, lines 57-63, Table 1, strain number 2057 and 2058; chart D;Chart E, last 4 strains,col. 8, oines 29-58) PolA is taught to be a temperature control replication gene that is induced at 32.degree. C. and below and causes DNA polymerase I to be non-functional at temperatures of 32.degree. C. and below

(i.e., "cold"sensitive) and is taught to be useful in conjunction with other essential gene mutations (col. 56, line 68), polA(CS)--causes DNA polymerase I not to function at temperatures below 32.degree. C. The combination of polA regulation together with an essential gene mutation results in a vast improvement in safety over that afforded by only using a single essential gene mutation alone. The reference suggests the use of delta-asd mutant and delta-thymidine mutants that are regulated.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to modify the invention of either one of Curtiss or Curtiss in view of the teachings of Curtis ('619) because Curtiss ('619) teaches that through the use of an environmentally responsive promoter, the expression genes do not express the heterologous protein at times when such expression would be undesirable, specifically during culture, vaccine preparation, or storage, contributing to the viability of the cells, but when administered to humans or animals, express large amounts of the protein. This is desirable because high expression of many heterologous proteins in Salmonella can be associated with toxicity to the bacterium. The use of only a single integrated copy of the DNA encoding the heterologous protein also contributes to minimal expression of the heterologous expression antigen at times when expression is not desired. In the absence of a showing of unexpected results the applied references obviate the now claimed invention because the prior art teaches that importance of utilizing more than one mutation for the microbial cell, especially regulation gene that are

environmentally controlled and would provide for safer immunogenic compositions especially when the cells are outside the animal host.

20. Claims 30-33, 35-38,50,52, 53 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtiss (US Pat.'345) in view of Molin et al (US Pat.'916) and Hershberger et al.

See discussion of **Curtiss in view of Molin (US '345)** above. The cited references discloses a method of inducing an immune response utilizing an avirulent Salmonella that comprises an expression gene that encodes and antigen under a temperature promoter or regulatory element but differs from the instantly claimed invention by failing to show the use of a temperature regulated promoter or regulatory element.

Hershberger shows and claims a extra chromosomal vector, that comprises a cI857 repressor in an analogous art for the purpose of producing an improved microbial cell that expresses a gene that encodes a gene for use in immunizing a warm blooded animal, and aids in defining mechanisms of environmental control through regulation of lethal markers and complimentary cloning vectors(col. 1, lines 50-60; claim 6, and claim 24)

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to modify the promoter and regulatory element of Curtiss with the regulatory element of Hershberger because Hershberger teaches a successful means and methods that stabilize and compliment environmentally limited viability systems through the production of

suicidal cells containing a lethal marker and a repressor on a recombinant DNA cloning vector and Curtiss shows the use of a complementary recombinant DNA cloning vector that comprises complementary gene for a marker on the microbial chromosome that is essential for cell viability, which upon repression, induces cell death. In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining a microbial cell system with increased stability that would evidence increased gene expression coupled with increased environmental safety ('815:col. 2, lines 1-22).

21. Claims 30,33, 36-44, 46, 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtiss(US Pat.5,840,483) in view of Youderian (1980).

Curtiss discloses an avirulent strain of Salmonella typhimurium, designated X3115 (see Table 1, col. 11) that is delta asd and comprises P22 bacteriophage genes. The cell contains lysogenic genes of P22(see co. 13, line 18, footnote "e"). An extrachromosomal gene that encodes the essential gene and stabilizes the microbial cell while in the host but would not be stable outside the animal. The reference discloses and teaches the microbial cells were administered (col. 31-40) to a warm blooded animal and have utility for immunizing individuals (abstract, second to last line) and to produce an immune response (see col. 2, line 32). Oral, mucosal administration of the microbial cells is taught to be one of the preferred modes of administration. The strains of Salmonella are bivalent and express an additional antigen for a second microbial cell. Strain X3115 comprises P22 and can be lethality killed due to host cell

lysis, as well as an essential gene asd for administration to a warm blooded animal, but the reference differs from the instantly claimed invention by failing to teach the specific genes that encode the lethality genes of P22.

Youderian et al disclose that gene 19 and gene 13 of P22 encode lysogenic products in an analogous art for the purpose of identifying the products produced by P22 genes.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made that Salmonella strain of Curtiss, X3115 that comprised P22, would encode both gene 19 and gene 13 of P22 because Curtiss discloses that the genes encoded lysogenic expressed products and Youderian teaches that gene 19 and gene 13 are the products produced by P22 to cause lysogenesis.

Conclusion

22. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

23. Curtiss et al(US Pat. 5,387,744; 5,656,488) teach a method of administering a microbial cell that comprises an expression antigen, wherein the microbial cell is an avirulent Salmonella strain with a promoter, and attenuated through asd, cya mutations.

24. Curtiss III (US Pat. 5,855,879) is cited to show the use of P22int bacteriophage in the transformation of Salmonella attenuated strains that express a heterologous antigen.

25. Curtiss III (US Pat. 5,468,485) is cited to show asd mutant strains of avirulent Salmonella.

26.Clarke et al is cited to show a DAP mutant of Salmonella for vaccination of calves.

27. Chakravorty et al (1974) is cited to show control of transcription of phage P22 infected host.

28. Youderian et al (1980) is cited to show a microbial cell, Salmonella typhimurium, that comprises P22 genes 13 and 19 that are induced by heat induction (see page 260, col. 1, paragraph 2, and Figure1).

29. Tian et al (1992) is cited to show Salmonella Asd negative mutant that expresses Cholera toxin B in a host to stimulate an immune response.

30. Schodel et al (1994) is cited to show Salmonella expressing hepatitus B virus core antigen as a candidate oral vaccine composition.

31. Stewart (1989) is cited to show the use of P22 bacteriophage for the transformation of Salmonella typhimurium with lux genes.

32. Bermudes et al (US Pat. 6,080,849) is cited to show genetically modified tumor targeted bacteria with reduced virulence.

33. Semerjian et al is cited to show the genetic structure of the P22 PL operon.

34.Miller et al (1989) is cited to show bacteriophage P22 as a vehicle for transducing cosmid gene banks of Salmonella.

35.Rennell et al (1985) is cited to show P22 lysis genes.

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner

can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp August 17,2000

Patricia A. Duffy
PATRICIA A. DUFFY
PRIMARY EXAMINER